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An anti-oxidant preparation based on plant extracts for the treatment of circulation and adiposity problems

The present invention relates to a preparation based on plant extracts which has an anti-oxidant effect and is particularly useful in the treatment of circulation problems such as phlebitis, varicose veins, arteriosclerosis, haemorrhoids and high blood pressure, as well as in the prevention and treatment of surplus fat.

The object of the invention is to provide a preparation to be taken orally, based on a combination of active ingredients of natural and plant origin, which work more effectively to prevent and treat the aforesaid problems when administered by mouth.

This object is achieved according to the invention by providing a preparation characterised in that its active ingredients include a combination of *Ginkgo biloba* biflavones, catechine and/or epicatechine, cumarine and derivatives thereof, iodine and an ingredient chosen from asiaticoside, asiatic acid, madecassic acid and compounds thereof.

The preparation is obtained by mixing plant extracts which contain the above active components.

It is known that extracts from the leaves of *Ginkgo biloba* contain important active components and in particular flavonol glucosides, lactonic terpenes and dimeric biflavones or flavones. The flavonol glucosides and the lactonic terpenes constitute the active components of the standardized *Ginkgo biloba* extracts currently available on the market;

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however these extracts do not contain the biflavone component which is not extracted during normal processing. The *Ginkgo biloba* extract used in compositions according to the present invention is highly enriched with the biflavone component and, as a possible option, with extracts containing flavonol glucosides and lactonic terpenes. Five biflavones in particular have been identified in the biflavone component of *Ginkgo biloba*: these are, in particular, amentoflavone, bilobetine, isoginkgetine, ginkgetine and sciadopisidine; the five said compounds differ only by the presence of methyl groups in some positions and, like all flavones, are powerful antioxidants. However, from a pharmacological point of view, they are characterised by their anti-phosphodiesterase, anti-inflammatory, vasculokinetic and anti-allergy properties. Phosphodiesterases (PDE) are cellular enzymes responsible for interacting with cyclic nucleotides so as to linearize them. Cyclic nucleotides are involved as second messengers in transmitting intercellular signals and are thus responsible for some phenomena which are very important from a biochemical point of view. They assist with the visual process and in the relaxation of smooth muscles, they stimulate lipolysis in adiposity and vasculo-motion in capillary arterioles. More specifically, it is sufficient to report that in inhibiting PDE depending on cyclic AMP, these biflavones demonstrate an IC₅₀ of 1.2 micromoles.

The anti-inflammatory properties of biflavones, and in particular those of amentoflavone, have been demonstrated both in vitro, by measuring the interaction of these biflavones with cyclo-oxygenase, lipo-oxygenase and phospholipase A₂, and in vivo, using various models of inflammation in animals (carrageneen oedema, Croton oil inflammation etc). The anti-inflammatory action of the biflavones was confirmed

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both in models using local application and in those in which they were administered peritoneally. In these models, the biflavones always demonstrated an anti-inflammatory action equivalent to that of indomethacyn or prednisolone. This effectiveness can be explained by analysing the IC50 of cyclo-oxygenase inhibition, which for amentoflavone is 3 micromoles.

With regard to the microvasculokinetic activity of biflavones, it should be reported that, following acute treatment, these substances improve the size of the arterial sphygmie wave and, following chronic treatment they improve capillary density in tissues with trophic-connective problems, such as those affected by panniculopathy and/or various degrees of sclerodermy. Biflavones also have clear anti-allergy properties; they inhibit the release of histamine by mast-cells stimulated by allergens.

In the context of the present invention, it has been demonstrated that, when administered orally, the activity of the aforesaid biflavones, possibly in combination with flavonol glucosides and lactonic terpenes which are normally present in standard *Ginkgo biloba* extracts, is enhanced when the latter are combined with the aforesaid active compounds.

The extracts are preferably used in a phytosomal form, in which the active components are compounded with phospholipids.

In the context of the invention it is convenient to use an extract of leucocyanidine or leucoanthocyanine derived from *Vitis vinifera* as the source of catechine or epicatechine. Leucoanthocyanines are procyanidolic oligomers derived from

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condensing monomeric units of flavan-3-ols and flavan-3,4-diols, these being either free or esterified with gallic acid. Leucocyanines are powerful anti-oxidant substances with the ability to protect capillaries by increasing oxygen to the tissue; these active substances prove biologically active even when administered orally and they have been shown to be tropic for the cardio-vascular system and for all tissues, such as artery walls, which are rich in glucoaminoglycene. Preferably, phytosomal forms of extracts are used, thus further enhancing the bioavailability of the active principles. In this form the procyanodines are completed with phospholipids, particularly distearylphosphatidylcholine of soya.

The preferable source of coumarin is an extract of *Melilotus* (*Melilotus officinalis*), coumarin and its derivatives being the main active ingredients thereof; the main active ingredients of this extract are melilotine (3,4 dihydro-coumarin), melilotic acid (hydroxycoumarinic acid), melilotoxide (a melilotine glucoside) and some flavinoids which act like vitamin P; the active ingredients contained in the extract are particularly effective in increasing capillary strength, in reducing vascular permeability, in stimulating venous circulation and improving lymphatic circulation.

Extract of *Melilotus* may be replaced or backed up, as a source of coumarin and its derivatives, by an extract of *Aesculus hippocastanum* (horse chestnut) in the same dosage or up to around twice the dose of *Melilotus* extract.

The most abundant active principle of *Aesculus hippocastanum* extract, obtained from the bark, the pericarp of the fruit,

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the leaves or the buds, is coumarine glucoside, esculoside (6-0-glucosil-7-hydroxy-coumarine). Other coumarines contained in the extract are fraxine (8-0-glycoside-7-hydroxy-6-metoxycoumarine) and the aglicones, esculetin (6,7-dioxy-coumarine) and fraxetine (7,8-dioxy-6-methoxy-coumarine).

The preferred source of asiaticoside, asiatic acid and madecassic acid is an extract containing a triterpenic fraction of centella (*Centella Asiatica*) which contains a combination of the above three active principles. The extract should preferably be used in a phytosomal form, obtained by a reaction between the triterpenic fraction of *Centella Asiatica* with a phospholipid. A main action of the triterpenic fraction of centella consists in accelerating the uptake and metabolism of lysine and of proline, thus increasing the synthesis and the release of tropocollagen and stimulating the turnover of acid mucopolysaccharide acids in connective tissue. Thanks to these properties, the active principles are particularly effective in reducing localised adiposity.

The preferred source of iodine is an extract of *Fucus vesiculosus*, a seaweed of the Fucaceae family. The role of the iodine in *Fucus vesiculosus* is currently well characterised; it is made more readily available by complexing with a protein fraction of the extract; it increases the synthesis of thyroid hormones and indirectly enhances the lipolytic action of these hormones (T3 and T4) thanks to a local thermogenic action on adipose tissue. The *Fucus* extract also contains polysaccharides such as fucoidin, alginic acid, laminarin and poliose; of these, the alginic acids, in particular, enhance the effect of the extract since they are hydrophilic molecules able to swell from their

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original volume in the presence of water; thanks to this characteristic, when ingested they not only reduce the appetite but also increase the speed of transit of food through the intestines, thus ensuring that it is less well absorbed.

The basic composition of the invention can thus be obtained by mixing a biflavone extract of *Ginkgo biloba* (perhaps in combination with a standard *Ginkgo biloba* extract also containing flavonol glucosides and lactonic terpenes), leucocyanidine extract, Melilotus extract, Centella extract and extract of *Fucus vesiculosus*; these extracts preferably being in a phytosome form.

With reference to the extracts normally available on the market, the basic composition is preferably made up by the following percentages by weight:

- 1.5 - 32% biflavone extract of *Ginkgo biloba*;
- 6 - 80% of leucocyanidine extract;
- 1.5 - 60%, preferably 1.5 - 32% of melilotus extract and/or *Aesculus hippocastanum* extract;
- 1.5 - 32% of centella extract;
- 1.5 - 85% *Fucus vesiculosus* extract, possibly in combination with:
 - 1.5 - 32% of standard *Ginkgo biloba* extract containing flavon glucosides and lactonic terpenes.

In terms of the content of active principles, the composition of the invention preferably contains the following percentages by weight:

- 0.2 - 12%, preferably 0.5 - 6% of total biflavones, expressed as ginkgetine content;

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0.2 - 12%, preferably 0.5 - 8% of catechine and/or epicatechine, expressed as catechine content;

0.15 - 7%, preferably 0.3 - 3.5% of cumarine and its derivatives;

0.25 - 15%, preferably 0.5 - 7.5% of asiaticoside;

0.25 - 22%, preferably 0.5 - 11 % of asiatic acid and/or madecassic acid;

up to 0.5% of iodine and possibly one or more of its components:

0.25 - 12%, preferably 0.5 - 6%, of flavonol glucosides, and

0.1 - 2%, preferably 0.2 - 1% of Ginkgolide lactonic terpenes (bilobalide).

The composition can also contain active ingredients chosen from methylxanthinic derivatives, such as caffeine, theobromine or theophylline in particular; mono and di-caffeoylchinic acids, chlorogenic acids, eicosapentaenoic acid (EPA), docahexaenoic acid (DHA) gamma-linolenic acid and combinations thereof.

The preferred source of methylxanthinic derivatives, of caffeine and of chlorogenic acids in particular, is an extract of *Ilex paraguariensis*, possibly in phytosomal form; the standard, commercially available extract can be added to the previously-described basic mixture in a quantity of 1.5 to 32% by weight.

Caffeoylchinic acid and its derivatives (such as cynarine) are preferably introduced by means of an artichoke extract (*Cynara scolymus*); this extract typically also contains caffeic acid and chlorogenic acid; this extract is preferably

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used in quantities of 1.5 to 32% by weight with reference to 100 parts of the basic mixture.

The preferable source of eicosapentaenoic acid (EPA) and of docohexaenoic acid (DHA) is fish oil which, with reference to 100 parts of the basic mixture, may be added in quantities of 5 to 80% by weight.

Gamma-linolenic acid is preferably introduced into the formulation by the use of borage oil, added in quantities of 30 to 120% by weight with reference to 100 parts of basic preparation.

In particular, in the preferred embodiment of the invention, the composition includes one or more of the following components:

Caffeine in quantities of 0.05 to 2.5 (preferably 0.1 - 1%) by weight with reference to the total preparation,

Caffeoylchinnic acids in quantities from 0.05 to 4.8% (preferably 0.01 to 2.5%) by weight,

Eicosapentanoic acid in quantities from 0.75 to 24% (preferably from 1.5 to 12%) by weight,

Docohexanoic acid in quantities from 0.6 to 8% (preferably 1.2 to 4%) by weight,

Gamma-linolenic acid in quantities from 2.5 to 22%, preferably 5-11% by weight.

For example, a typical composition could be formulated according to the data in the table below, which gives the preferred minimum and maximum quantities expressed in parts by weight of the components of the basic mixture (marked with an asterisk) and of optional ingredients.

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	Minimum (Parts by weight)	Maximum (Parts by weight)
*Dry extract of <i>Vitis vinifera</i> (optionally phytosomes)	20	200
*Dry extract of <i>Melilotus officinalis</i> and/or <i>Aesculus hippocastanum</i>	5	40
* <i>Ginkgo biloba</i> biflavones (optionally phytosomes)	5	50
Dry extract of <i>Ginkgo biloba</i> (optionally phytosomes)	5	50
*Dry extract of <i>Fucus vesiculosus</i>	50	200
*Dry extract of <i>Centella asiatica</i> (optionally phytosomes)	10	50
Dry extract of artichoke	10	100
Dry extract of <i>Ilex paraguariensis</i>	10	100
Borage oil	50	1000
Fish oil	50	750
Soya lecithin	20	100

In the above table, the given values, expressed in parts by weight, correspond, when expressed in milligrams to the minimum and maximum daily doses recommended or to the dose per capsule.

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The composition of the invention is formulated in forms suited to be taken orally, such as, for example, gelatin capsules with either soft or rigid shells, tablets, pills, elixirs, suspensions and syrups. The various forms can include excipients and/or binders and/or pharmaceutically acceptable vehicles, in particular lecithin mono- and diglycerides of fatty acids. The mixture of extracts can be administered orally, possibly in an edible vehicle or can be incorporated directly into food as part of a diet.

The preparation is particularly useful in treating localised adiposity, in particular in men but also in women. It is well known that adiposity differs in men and in women, by the area in which it is deposited, by the quantity, by functional response and by consequences for health; in actual fact this surplus fat ("spare tyres" in men and cellulite in women) is due, at least in part, to a tropism which is known to involve both vascular and connective tissue, as well as adipose tissue. The composition of the invention provides an association of well characterised substances from a pharmacotoxicological and chemical point of view, which is totally free of side effects and is particularly advantageous compared to pharmaceutical preparations based on appetite-suppressant compounds, as used in conventional pharmacological treatment.

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CLAIMS

1. A composition based on plant extracts, with an anti-oxidant activity which is particularly useful in the prevention and treatment of circulation problems and in the prevention and treatment of adiposity, characterised in that its active ingredients comprise, in association, biflavones of *Ginkgo biloba*, catechine and/or epicatechine, cumarine or derivatives thereof, iodine and a component chosen from among madecassic acid, asiatic acid, asiaticoside and mixtures of these.
2. A composition according to Claim 1, characterised in that it is obtained by mixing plant extracts containing the aforesaid active principles.
3. A composition according to Claim 2, characterised in that the said extracts are in phytosomal form.
4. A composition according to any one of the preceding Claims, characterised in that it further includes flavonol glucosides and lactonic terpenes.
5. A composition according to any Claim from 1 to 4, characterised in that it also includes an active principle chosen from the group consisting of methylxanthinic derivatives, chlorogenic acids, mono- and di-caffeoylchinnic acid and derivatives thereof, eicosapentaenoic acid, docohexaenoic acid, gamma-linolenic acid and mixtures thereof.

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6. A composition according to any of Claims 1 to 4, characterised in that it is obtained by mixing plant extracts in the following percentages by weight:

- 1.5-32% of *Ginkgo biloba* biflavone extract;
- 6-80% of leucocyanidine;
- 1.5-32% of *Melilotus* and/or *Aesculus hyppocastanum* extract;
- 1.5-32% of centella extract;
- 1.5-85% extract of *Fucus vesiculosus*; and optionally
- 1.5-32% of standardised *Ginkgo biloba* extract containing flavone glucosides and lactonic terpenes.

7. A composition according to Claim 6, characterised in that with reference to 100 parts of the basic mixture of Claim 6, it also includes one or more of the following components:

- from 1.5 to 32% by weight of *Ilex paraguariensis* extract;
- from 1.5 to 32% by weight of artichoke extract;
- from 5 to 80% by weight of fish oil;

and

- from 30 to 120% by weight of borage oil.

8. A composition according to any one of the preceding Claims which includes:

- 0.12-12%, preferably 0.5-6% by weight, of total biflavones;
- 0.2-12%, preferably 0.5-8% by weight, of catechine and/or epicatechine;
- 0.15-7%, preferably 0.3-3.5% by weight, of coumarins and derivatives thereof;
- 0.25-15%, preferably 0.5-7.5% by weight of asiaticoside;

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0.25-22%, preferably 0.5-11% by weight, of asiatic acid and/or madecassic acid;

up to 0.5% of iodine and, optionally

0.25-12%, preferably 0.5-6% by weight, of flavonol glucosides and

0.1-2%, preferably 0.2-1% by weight, of lactonic terpenes.

9. A composition according to Claim 8, characterised in that it also includes one or more of the following components:

from 0.05 to 2.5%, preferably 0.1-1% by weight, of caffeine;

from 0.05 to 4.8%, preferably 0.1-2.5% by weight, of caffeilchinic acids;

from 0.75 to 24%, preferably 1.5-12% by weight, of eicosapentaenoic acid;

from 0.6 to 8%, preferably 1.2-4% by weight, of docoesaenoic acid; and

from 2.5 to 22%, preferably from 5 to 11% by weight of gamma-linolenic acid.

10. A composition according to any one of the preceding Claims in a pharmaceutical form for oral administration.

11. The use of flavone dimers in the formulation of a preparation based on plant extracts useful in the prevention and treatment of circulation problems and adiposity.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
P, X	W.REILLY, V.REEVE: "Body contouring using an oral herbal antioxidant formulation-Centelapulus: a dose controlled observational study" REDOX REPORT, vol. 5, no. 2-3, 2000, pages 144-145, XP000990069 page 144	1,2,5, 10,11
A	GB 2 174 904 A (SEUREF) 19 November 1986 (1986-11-19) claims 1,3,4,6	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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